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ORIGINAL ARTICLE

Validated chromatographic methods for the simultaneous determination of Mometasone furoate and Formoterol fumarate dihydrate in a combined dosage form

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Abstract Two chromatographic methods were developed and validated for the simultaneous determination of Mometasone furoate (MO) and Formoterol fumarate dihydrate (FOR). Combination of MO and FOR is used for the treatment of asthma in patients suffering from reversible obstructive airway disease. The first chromatographic method was based on using aluminum TLC plates pre-coated with silica gel GF_{254} as the stationary phase and chloroform:ethyl acetate: methanol:toluene:formic acid (5:2:2:2:0.1, by volume) as the mobile phase followed by densitometric measurement of the separated bands at 233 nm. The second method is a high performance liquid chromatographic method for the separation and determination of MO and FOR using reversed phase C_{18} column with isocratic elution. The mobile phase composed of methanol: 0.5% ammonium acetate pH adjusted with acetic acid (80:20, v/v) at a flow rate of 1.0 mL/min. Quantitation was achieved with UV detection at 220 nm. The specificity of the developed methods was investigated by analyzing the pharmaceutical dosage form. The validity of the proposed methods was assessed using the standard addition technique. The obtained results were statistically compared with those obtained by the reported methods, showing no significant difference with respect to accuracy and precision at $p = 0.05$.

1. Introduction

Asthma is a chronic inflammatory disorder of the airways. During asthma attacks, the smooth muscle cells in the bronchi constrict, the airways become inflamed and swollen, and breathing becomes difficult.[1] Therefore one of the ways of treating it is a combination of inhaled corticosteroids to reduce the inflammation of the airways and prevent the loss of lung functions[2] with long acting β2 agonists (LABA) which acts locally on the lung as a bronchodilator and relaxes muscles

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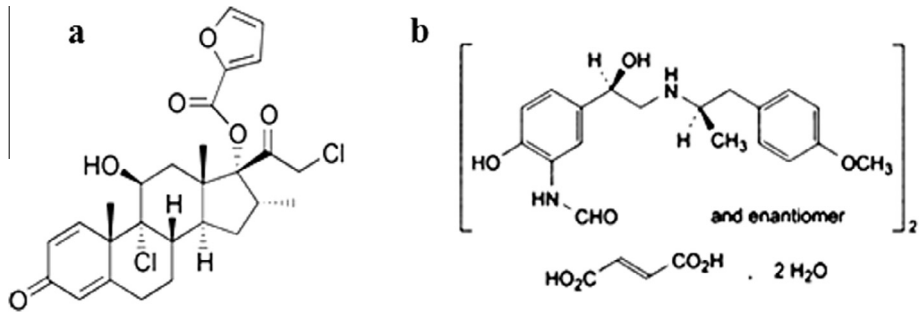

Figure 1 Structural formula of (a) Mometasone furoate MO and (b) Formoterol fumarate dihydrate FOR.

in the airways to improve breathing. An example of this combination is Mometasone furoate (MO), (9α,21-dichloro-1 1β,17-dihydroxy-16α-methylpregna-1,4-diene-17-yl furan-2-carboxylate) (Fig. 1a) which acts as a corticosteroid and Formoterol fumarate dihydrate (FOR), (N-[2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino] ethyl]phenyl]formamide(E)-butenedioate dehydrate) (Fig. 1b) which acts as a long acting β2 agonist.[3]

Literature survey reveals that MO and FOR are official drugs in European Pharmacopoeia,[4] also MO is official in United States Pharmacopoeia.[5] Several analytical methods have been reported for the determination of MO alone or in combinations with other drugs including, spectrophotometry,[4,6–9] TLC[10,11] and HPLC.[5,12–20] Besides, several methods have been reported for the determination of FOR alone or in combinations including, non aqueous titration,[4] spectrophotometry,[21–24] voltammetry,[25] capillary electrophoresis,[26] and HPLC.[18–20,27–32] The aim of this work is to develop simple chromatographic methods for the simultaneous determination of MO and FOR in pharmaceutical dosage form.

2. Experimental

2.1. Instruments

The thin-layer chromatographic (TLC) system consisted of a Camag Linomat autosampler (Muttenzl, Switzerland), a Camag microsyringe (100 μL) and a Camag 35/N/30319 TLC scanner with winCATS software; an ultraviolet (UV) lamp with a short wavelength at 254 nm (Desaga, Wiesloch, Germany); and TLC plates precoated with silica gel GF_{254} 10 × 20 cm, 0.25 mm thickness (Merck, Darmstadt, Germany).

Shimadzu HPLC system consisted of a pumping system (model LC-10 AD vp), an ultra-violet variable wavelength detector (model SPD-10A vp), Degasser (model DGU-12A) and System controller (model SCL-10A vp) Equipped with a prominence autosampler (model SIL-20A) (Shimadzu, Kyoto, Japan). An Inertsil ODS-3 column (5 μm, 250 mm × 4.6 mm i. d.) was used as stationary phase (GL Sciences, Tokyo, Japan).

2.2. Materials and reagents

2.2.1. Pure standard

Mometasone furoate was kindly supplied by SIGMA Pharmaceutical Industries, Cairo, Egypt, its purity was found to be 100.12 ± 0.762 according to the official method.[5]

Formoterol fumarate dihydrate was kindly supplied by NOVARTIS pharmaceuticals, Cairo, Egypt, its purity was found to be 100.02 ± 0.592 according to the reported method.[19]

2.2.2. Pharmaceutical dosage form

Dulera® Inhalation aerosol (Batch No. GLG122) labeled to contain 100 μg of MO and 5 μg of FOR per actuation, was manufactured by (MERCK & CO. INC, White House Station, USA) and obtained from the American market.

2.2.3. Chemicals and reagents

All chemicals used throughout the work were of analytical grade and solvents for HPLC were of HPLC grade. These included methanol (Sigma-Aldrich, Belgium), chloroform (Sigma-Aldrich, Belgium) and double distilled deionized water (Otsuka, Cairo, Egypt). Ethyl acetate, toluene, formic acid and ammonium acetate were purchased from Al-Nasr Pharmaceutical Chemicals Co., Cairo, Egypt.

2.2.4. Standard solutions

- Standard stock solution of MO: 1.0 mg/mL in methanol.
- Standard stock solution of FOR: 1.0 mg/mL in methanol.

2.2.5. Working Solutions

For TLC-spectrodensitometric method: Working solution of FOR (200 μg/mL) was prepared from its stock solution using methanol as a solvent.

For HPLC method: Working solutions of MO (400 μg/mL) and FOR (100 μg/mL) were prepared from their respective stock solutions using mobile phase as a solvent.

2.3. Procedures

2.3.1. Construction of the calibration curves

2.3.1.1. For TLC-spectrodensitometric method. Accurately measured aliquots of MO stock standard solution (1 mg/mL) and FOR working solution (200 μg/mL) were spotted onto TLC plates using Camag Linomat autosampler with microsyringe (100 μL). The plates were then developed by the ascending technique using chloroform:methanol:ethyl acetate:toluene:formic acid (5:2:2:2:0.1, by volume) as a mobile phase. The plates were then removed and air-dried. The chromatogram was scanned at 233 nm. Calibration curves representing the relationship